REMARKS

Status of Claims:

Claims 1-4, 7, 8, 11-13, 16, 17, 20, and 21 are currently pending in the application.

No amendments to the claims have been made in this Response.

Priority:

The Examiner has clarified that he has ***not*** denied Applicants' claim of foreign priority GB0121285.1, i.e., that he ***has granted*** this priority claim. Applicants appreciate the Examiner's clarification of this issue.

35 U.S.C. § 103(a) – Obviousness Rejection:

The Examiner has rejected claims 1-4, 7, 8, 11-13, 16, 17, 20, and 21 under 35 U.S.C. § 103(a) for obviousness over **Siemann et al.**, "Enhanced Antitumor Efficacy Through the Combination of Vascular Targeting Agents and Conventional Anticancer Drugs," *Proc. American Ass'n Cancer Research* 41:525 (2000) ("Siemann") in view of **Pruijn et al.**, "Mechanisms of Enhancement of the Antitumour Activity of Melphalan by the Tumour-Blood-Flow Inhibitor 5,6-Dimethylxanthenone-4-Acetic Acid," *Cancer Chemother. Pharmacol.* 39(6):541-546 (1997) ("Pruijn") and **van Moorsel et al.**, "Combination Chemotherapy Studies with Gemcitabine and Etoposide in Non-Small Cell Lung and Ovarian Cancer Cell Lines," *Biochem. Pharmacol.* 57(4):407-415 (1999) ("van Moorsel").

With regard to this obviousness rejection, Applicants respectfully submit that the Examiner's bases for obviousness are not sufficient to support this rejection. Specifically, there are five fundamental deficiencies/flaws with the Examiner's position:

- First, the Examiner's assertion fails to appreciate the clear distinction between what is ***possible*** and what is ***expected***;
- Second, the Examiner's rationale fails to acknowledge and address the numerous reasons (particularly the very unpredictable results seen for combinations of DMXAA with anti-metabolites) why synergy would not necessarily have been expected between DMXAA and gemcitabine;
- Third, the Examiner statements provide no motivation whatsoever for combining the cited references, as Applicants previously stated in their last Response and now supplement with additional arguments in the present Response;
- Fourth, the Examiner's asserted "natural presumption" for combining anticancer drugs is, respectfully, mere hindsight reasoning that is not supported by logic or by literature references already cited by Applicants in their previous Response, with further references now provided in the current Response; and,
- Fifth, in co-pending case 10/946,833, which is also directed to the use of the DMXAA of the invention, the Examiner has explicitly stated in the 5/22/07 Office Action for that case that "***the use of DMXAA in the treatment of tumors, particularly for use in humans, is extremely unpredictable***" (emphasis added). See page 11 of the Office Action of 5/22/07 for co-pending case 10/946,833. This statement by the Examiner in this co-pending case directly contradicts the Examiner's conclusion in the present case that the combination is ***predictable***. Since a statement and its opposite cannot both be true, Applicants request that the Examiner clarify which of these contradictory statements the Examiner wishes to espouse.

Applicants address each of these fundamental deficiencies/flaws in more detail below. Applicants respectfully state that the Examiner must specifically respond to each of these five noted deficiencies/flaws in order to avoid a situation in which the error that results from the Examiner's failure to address these noted deficiencies/flaws creates a situation which

affects the ability of the Applicants to reply to the Office Action in which the Examiner has not addressed these issues. See MPEP § 710.06.

Deficiency/Flaw 1: The Distinction Between *"Possible"* And *"Expected"*:

The Examiner has made a number of unsupportable allegations in crafting this obviousness rejection. In particular, on page 5 of the Final Office Action (mailed June 11, 2007), the Examiner makes the following assertion:

> The fact that the Applicants have shown that a combination of DMXAA and gemcitabine is synergistic **only demonstrates one of three expected results**. (Emphasis added.)

The Examiner is clearly confusing "***possible***" with "***expected***." That is, it is logically impossible for more than one of a set of mutually exclusive results to be "***expected***."

It is possible to assign a likelihood (i.e., a percentage chance of occurrence) to more than one outcome from a set of mutually exclusive outcomes. However, a likelihood is not the same as an expectation. In order for a person of ordinary skill in the art to "expect" an outcome, that particular outcome must (logically) be the ***only*** outcome that they expect. Here, as well as for all combinations of active ingredients, the possible and mutually exclusive outcomes are:

(i) antagonism (i.e., one active agent decreases the efficacy of the other);

(ii) additive action (i.e., the two active agents have no impact, either positive or negative, on each other's efficacy); and

(iii) synergy (i.e., the two active agents are more effective together than they are separately).

The Examiner has failed to set forth why it would have been "***expected***" that DMXAA would be synergistic with gemcitabine. Indeed, the Examiner has merely pointed to the following reasons to support the rejection:

(i) synergy seen between DMXAA and 86% of the other anti-cancer drugs recited in the present application;

(ii) synergy reported between DMXAA and various other anti-cancer agents reported in the prior art; and

(iii) an unsupported assertion that "DMXAA potentiates the antitumor effect of a number of anticancer agents . . . ***because of its mechanism of action (inhibiting tumor blood flow)***" (Final Office Action, at page 9).

With regard to the Examiner's first two points (above), it is perhaps not surprising that the literature (including patent literature) contains examples of combinations that are synergistic. This is on the grounds that scientific publications (and particularly patent applications) are overwhelmingly based upon ***positive results***. In other words, those working with particular active agents are unlikely to widely publicize (or attempt to patent) combinations that were found not to work.

In relation to the Examiner's third point (above), to date, it is still not understood precisely how DMXAA works (either alone or in combination with other anti-cancer agents). Thus, it is incorrect to state that knowledge of DMXAA's mechanism of action would have prompted the ordinarily skilled person to take any particular course of action.

In the absence of an understanding of DMXAA's mechanism of action, those skilled in the art would, as of the priority date of the present application, have been reduced to relying upon empirical observations.

Contrary to how the Examiner has characterized Applicant's position, Applicant has not asserted that only antagonism or additive action was possible in the case of combinations of DMXAA with other anti-cancer agents. Rather, Applicants submit that the synergism observed with gemcitabine is ***unexpected*** because those of ordinary skill in the art,

based upon their empirical observations of prior art combinations, would have had no reason whatsoever to expect to see such synergism.

Deficiency/Flaw 2: Specific Reasons Not To Expect Synergism

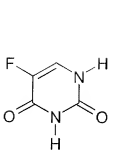
Gemcitabine is an anti-metabolite. This is quite unlike all of the other agents that have been demonstrated to act synergistically with DMXAA. Therefore, compared to these other agents, gemcitabine represents a different class of anti-cancer agent with a completely different mechanism of action.

In light of the above, those of ordinary skill in the art would have been stepping into unknown territory when combining DMXAA with an anti-metabolite. For this reason alone, prior to the disclosure of the present application, it would have been impossible for those of ordinary skill in the art to predict whether DMXAA would demonstrate synergy with anti-metabolites (their only prior knowledge relating to different classes of agents).

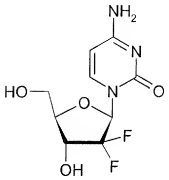
In addition to the above, there is a great deal of unpredictability in relation to combinations of DMXAA with other anti-cancer agents, particularly combinations with anti-metabolites. This is demonstrated amply by the data presented in the application as filed, which evidences the fact that 5-fluorouracil (another anti-metabolite) is actually ***antagonistic*** when used in combination with DMXAA. The structural and mechanistic similarities of 5-fluorouracil and gemcitabine are demonstrated below.

Gemcitabine and 5-fluorouracil (5-FU) are anti-metabolite cancer chemotherapy drugs with similar structures and mechanisms of action.

Structural Similarities: Both gemcitabine and 5-FU are fluorinated pyrimidine analogues. Gemcitabine is an analogue of deoxycytidine in which the 2' carbons are replaced by fluorides and 5-FU is a fluorinated analogue of uracil. Their structures are as follows:



5-FU



gemcitabine

Mechanisms of Action: Like other pyrimidine antagonists, gemcitabine and 5-FU are similar in structure to the normal nucleotides, which become the building blocks of DNA.

Both gemcitabine and 5-FU inhibit DNA synthesis in accordance with the following mechanisms:

(i) blocking the formation of normal pyrimidine nucleotides *via* enzyme inhibition (thymidylate synthetase); and

(ii) interfering with DNA synthesis after incorporation into a growing DNA molecule.

By blocking DNA synthesis and repair, both gemcitabine and 5-FU make cells unable to replicate or repair, and thus ultimately cause cell death.

Further, both gemcitabine and 5-FU are prodrugs that require intracellular conversion to active phosphate metabolites for therapeutic efficacy. It is the triphosphates of both gemcitabine and 5-FU that compete with endogenous deoxynucleoside triphosphates for incorporation into DNA.

If, as the Examiner asserts, it would have been "expected" for DMXAA to demonstrate synergy with gemcitabine, then surely (given the great structural and functional

similarities between gemcitabine and 5-fluorouracil) such synergy would be equally "expected" with 5-fluorouracil. The fact that ***precisely the opposite*** result (antagonism) is seen with 5-fluorouracil demonstrates the fact that the Examiner is taking an overly simplistic (and ***hindsight***) view of the technical situation.

In summary, in light of the arguments presented above, the Examiner has not presented sufficient evidence to support the requirements of a finding of obviousness under 35 U.S.C. § 103(a), and the rejection of the claims on this basis must be withdrawn.

Deficiency/Flaw 3: No Motivation To Combine The References:

The Examiner has provided three bases for combining the references cited: 1) the statement made in the case *In re Kerkoven*, as cited in MPEP § 2144.06, that "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ..." (see the current Office Action, page 4, lines 1-3); 2) that regardless of *Kerkoven*, "motivation comes ***explicitly*** from the cited references" (emphasis added) (see the current Office Action, page 4, lines 1-3); and, 3) that motivation comes from the fact that:

> ... the prior art is ***replete*** with examples of chemotherapeutic drugs being combined to treat cancer. As such, it is not seen as inventive to combine DMXAA and gemcitabine, both of which were known in the art as anticancer treatments and both of which have been combined with other anticancer agents.

(emphasis in original) (see the current Office Action, page 4, lines 9-12).

With regard to the first of these bases for motivation, that the logic of *Kerkoven* applies to the present combination of chemotherapeutics, as Applicants have already stated in the last Response, this statement is, respectfully, an example of *reductio ad absurdum*, i.e., reduction to absurdity. In making this statement, Applicants intend no disrespect: the term is a term of art that refers to a logical argument that is untenable because

the logical construct that might have been valid in more limited circumstances has ***broken down*** for the facts to which it has been applied.

Thus in the present case, as Applicants explained at great length in their previous Response (the contents of which are all explicitly incorporated by reference in the present Response), unlike in *Kerkoven* or any of the other cases cited in MPEP § 2144.06, the chemotherapeutics of the present invention are novel combinations of non-interchangeable compounds, not compounds that are "so notoriously well known as to be capable of being taken [in combination merely] by official notice" (see Applicants Response of 4/16/07, page 8, citing *In re Crockett*), as is the case in *Kerkoven*, which involved a mere combination of two conventional ***spray-dried detergents***.

In the present Office Action, the Examiner has not addressed this argument, and has instead stated that "*Kerkoven* is not relied upon to provide the motivation to combine in the instant case." See Office Action, page 4, lines 6-7. Therefore, Applicants presume that the Examiner ***no longer asserts a motivation to combine the cited references on the basis of Kerkoven***. In this regard, Applicants request that the Examiner explicitly confirm this presumption, in order to avoid a situation in which the error that results from the Examiner's failure to respond to this request creates a situation which affects the ability of the Applicants to reply to the Office Action in which the Examiner has not addressed these issues. See MPEP § 710.06.

With regard to the second of the Examiner's stated motivations for combining the cited references, that "motivation comes ***explicitly*** from the cited references" (emphasis added), Applicants see no indication in the Office Action of the location(s) of this/these explicit statement(s) in the cited reference(s). Therefore, Applicants request either that the Examiner clarify his statement by providing this/these location(s) or withdraw his assertion that there is any support for a motivation to combine on this basis. In this regard, Applicants respectfully note that such clarification or withdrawal of this basis is necessary in order to avoid a situation in which the error that results from the Examiner's failure to provide such

clarification/withdrawal of this basis creates a situation which affects the ability of the Applicants to reply to the Office Action in which the Examiner has not addressed these issues. See MPEP § 710.06.

With regard to the third of the Examiner's bases for a motivation to combine the references, that "the prior art is ***replete*** with examples of chemotherapeutic drugs being combined to treat cancer" (emphasis in original) such that it is not inventive to combine the chemotherapeutics of the invention, Applicants respectfully state that this observation is not sufficient basis for a finding of motivation, since it is nothing more than, at best, an invitation to try combining compounds, which, in and of itself, is not sufficient for a finding of obviousness.

On the basis of all of the above, Applicants respectfully submit that the Examiner has not shown motivation to combine the cited references, that there is therefore no basis for a finding of obviousness, and that the rejection on this basis must therefore be withdrawn.

Deficiency/Flaw 4: The Examiner's "Natural Presumption" For Combining Anticancer Drugs Is Mere Hindsight Reasoning Rather Than An Actual Motivation To Combine The Cited References:

In the present Office Action, the Examiner has again stated that there is a "'natural presumption' that two known anticancer drugs would, when combined, provide a third composition also useful for treating cancer." See Office Action, page 4, lines 14-15. In responding to this statement as made in the previous Office Action, Applicants asked that "the Examiner explain the basis of this 'natural presumption' in light of, for example, the well-known *adverse* or even *lethal* effects of many anticancer drugs" (emphases in original) (see Applicants previous Response, page 9), and cited an article showing severe hand-foot syndrome resulting from a combination of two chemotherapeutics as an example of such adverse/lethal effects.

In the present Office Action the Examiner asks that "Applicants provide more than the ***single*** cited article to rebut this natural presumption" (emphasis in original) (Office Action, page 4, line 16). In compliance with this request, Applicants attach two additional references: an article entitled "*NSCLC Revisited: Single-Agent or Combination Therapy?*" by Robert S. Mochamuk; and a second article entitled "*Promising New Drug Uses Antibody Targeted Chemotherapy To Fight Leukemia,*" which is from Science Daily, December 10, 1998. In the first of these articles the statement is made that "Adverse effects were ***predictably*** more significant for the combination chemotherapy arm … [than] in the single-agent arm" (emphasis added) (bottom of first page of article), while in the second article the statement is made that the chemotherapeutic agent CMA-676 "is administered as a single agent, in contrast with chemotherapeutic regiments that involve multiple drugs ***that increase the likelihood of adverse side effects and drug-drug interactions***" (emphases added) (bottom of article).

Both of these highlighted statements clearly indicate that there is no "natural presumption" that one of ordinary skill would have that combination chemotherapeutics would not exhibit adverse side effects or adverse drug-drug interactions. These statements therefore refute the Examiner's "natural presumption" that there would be motivation to combine any two chemotherapeutics.

Perhaps more significantly, they also highlight the fact that the Examiner's "natural presumption" is, respectfully, mere hindsight analysis. Specifically, as Applicants stated earlier in this Response,

> … scientific publications (and particularly patent applications) are overwhelmingly based upon ***positive results***. In other words, those working with particular active agents are unlikely to widely publicize (or attempt to patent) combinations that were found not to work.

This statement applies with equal or greater force to combinations that have significant *adverse* or even *lethal* effects. Thus the Examiner's survey of the literature for working

combinations of chemotherapeutics generally reveals exactly and only that: ***working*** combinations. But no conclusion can be drawn on the basis of this survey by the Examiner that ***all***, ***many***, or even ***most*** combinations work, and certainly no conclusion regarding any motivation to combine based on working examples only against an unknown number of non-working examples. Thus, on this basis, reaching such a conclusion regarding the specific combination of the present invention is, respectfully, merely impermissible hindsight.

In this regard, Applicants respectfully note that the "natural presumption" that any two cancer drugs can be combined to create a combination useful for treating cancer is also devalued by the simple observation that, despite the large number of chemotherapeutic agents available, there are very few combination therapies relative to the number of potential combinations of single agents. Thus for example, Applicants refer the Examiner to the 56 (at the time of preparation of this Response) individual chemotherapeutic agents listed on cancerbackup.org.uk/Treatments/Chemotherapy/Individualdrugs. If the "natural presumption" of the Examiner were correct, one would reasonably expect 56x56 or 3,156 combination regimens, or some reasonable fraction of these 3,156 combinations. Instead, at the time of this writing, the same website shows only 46 combinations (see cancerbackup.org.uk/Treatments/Chemotherapy/Combinationregimen), i.e., ***1/100*** of the number expected based on the Examiner's "natural presumption." This result clearly indicates that the assertion that the Examiner makes that there is a "natural presumption" that any two "known anticancer drugs would, when combined, provide a third composition also useful for treating cancer" cannot be correct, i.e., that there is no motivation to combine that can be found based on the Examiner's arguments regarding this "natural presumption."

On the basis of all of the above, it is clear that the Examiner's "natural presumption" regarding the combination of agents of the present invention is incorrect, and that there is consequently no motivation to combine that this presumption supports. Therefore, on this basis, the obviousness rejection made by the Examiner should be withdrawn.

Deficiency/Flaw 5: The Examiner Finding of Obviousness In The Present Case is *Logically Impossible* In Light Of The Examiner's Own Statements of Unpredictability for the DMXAA Of the Invention As Made By The Examiner In Co-pending Case 10/946,833:

It is axiomatic that, if a statement is true, its opposite ***cannot*** be true. Therefore, a situation in which a statement and its opposite are ***both*** asserted to be true is, at the very least, a questionable situation that requires further – and detailed – explanation.

In the present Office Action the Examiner has stated that there is a "'natural presumption' that two known anticancer drugs would, when combined, provide a third composition also useful for treating cancer." See the Office Action, page 4, lines 14-15. Thus the Examiner has essentially stated that it is ***predictable*** that the compounds of the invention, when combined, would be effective in treating cancer, a conclusion regarding the Examiner's statements that is supported by the Examiner's further statement that "it is not seen as inventive to combine [the compounds of the invention] DMXAA and gemcitabine, both of which were known in the art as anticancer treatments and both of which have been combined with other anticancer agents."

With regard to this apparent statement of predictability, Applicants refer the Examiner to co-pending case 10/946,833, which is also directed to the use of the DMXAA of the invention, in which the Examiner has explicitly stated in the 5/22/07 Office Action for that case that "the use of DMXAA in the treatment of tumors, particularly for use in humans, is ***extremely unpredictable***" (emphasis added). See pages 10-11 of the Office Action of 5/22/07 for co-pending case 10/946,833. This statement by the Examiner in this co-pending case is at ***direct odds*** with what Applicants take to be the Examiner's statement of the ***predictable*** result of combination of DMXAA with other chemotherapeutics that the Examiner has asserted in the Office Action for the present case.

As discussed above, in a situation where a statement and its opposite are both asserted to be true, further explication is required. Therefore, Applicants request that the

Examiner explain exactly how the combination of DMXAA with other chemotherapeutics can be both predictable and unpredictable. In this regard, Applicants respectfully note that the such clarification is necessary in order to avoid a situation in which the error that results from the Examiner's failure to provide such clarification creates a situation which affects the ability of the Applicants to reply to the Office Action in which the Examiner has not addressed these issues. See MPEP § 710.06.

Nonstatutory Obviousness-Type Double Patenting Rejection:

The Examiner has provisionally rejected claims 1-4, 7, 8, 11-13, 16, 17, 20, and 21 for nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of co-pending U.S. Patent Application Serial No. 11/592,678 to Wilson et al. ("the '678 patent").

Applicants have submitted herewith a ***terminal disclaimer*** in compliance with 37 CFR § 1.321(c) and the required fee under 37 CFR § 1.20(d). Therefore, Applicants respectfully submit that this rejection is now obviated and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants submit that the rejections of the claims must be withdrawn and that the claims be allowed.

With regard to the statements by Applicants contained in this Response, Applicants respectfully submit that the Examiner address, ***at a minimum***, each of the five fundamental deficiencies/flaws raised by Applicants regarding the Examiner's Office Action in order to avoid a situation in which the error that results from the Examiner's failure to address these noted deficiencies/flaws creates a situation which affects the ability of the Applicants to reply to the Office Action in which the Examiner has not addressed these issues. See MPEP § 710.06.

Applicants also respectfully note that the Examiner has not completely updated his search of 11/8/06 in his most recent search of 6/5/07. Specifically, in his 11/8/06 search, the Examiner searched the EAST database, the STN database, and conducted a PALM Inventor Name search. However, in his 6/5/07 search, the Examiner updated only the PALM search. Applicants respectfully note that MPEP § 904.03 states that

> It is a prerequisite to a speedy and just determination of the issues involved in the examination of an application that a careful and comprehensive search, commensurate with the limitations appearing in the most detailed claims in the case, be made in preparing the first action on the merits so that the second action on the merits can be made final or the application allowed with no further searching ***other than to update the original search.***

(emphases added). Given the new changes to the Rules regarding the RCE/continuation practice, this complete updating has become even more important. Therefore, Applicants respectfully request that the Examiner update the results for his original search strings to ensure that no additional references are cited during prosecution, apart from those newly appearing in

the databases or as required by Applicants amendments to claims outside those already encompassed by the most detailed original claim(s) in the case.

The Commissioner is hereby authorized to charge $120 for a one-month extension of time, $130 for the accompanying terminal disclaimer, and any other time extension or other fee that may have been overlooked by Applicants, to Deposit Account No. 10-0223.

Respectfully submitted by,

Dated: 10/11/07

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NSCLC Revisited: Single-Agent or Combination Therapy?

Disclosures

Robert S. Mocharnuk, MD

Following the disappointing 4-arm ECOG trial results from a few years past that showed little difference among 4 modern doublet treatment schedules in advanced non-small-cell lung cancer (NCSLC), the clinical community has been somewhat at a loss to regroup. The incorporation of tyrosine kinase inhibitors like ZD1839 into standard NSCLC regimens seems to have rekindled some degree of enthusiasm, but at the same time has raised the issue of whether a "modern" single agent can hold its own with a "modern" cytotoxic 2-drug combination regimen.

This impetus for this reassessment comes in the wake of a recent meta-analysis of 25 trials involving 5156 patients with advanced NSCLC treated from 1974 to 1996, that demonstrated a 2-fold increase in response rate, a 3-fold increase in serious adverse side effects, and only a modest increase in overall survival. Dr. Rogerio Lillenbaum presented the results of a Cancer and Leukemia Group B (CALGB) trial comparing single-agent paclitaxel (225 mg/m^2 over 3 hours every 21 days) with standard combination paclitaxel (225 mg/m^2 over 3 hours) plus carboplatin (6 AUC) every 21 days.[1] Study goals included assessment of efficacy, quality of life, and cost-effectiveness in order to answer the question of whether combination therapy in these patients is "really worth it."

From October 1997 to January 2001, a total of 584 patients were enrolled, of which 561 were eligible by exclusion criteria. These patients were matched for a number of characteristics and the majority of tumors were adenocarcinomas. With a median follow-up of 19.7 months, the following results were observed (Table 1).

Table 1. Single-Agent vs Combination Chemotherapy in Advanced NSCLC

Treatment Regimen	Paclitaxel	Paclitaxel + Carboplatin
Patient number	277	284
Complete response	2%	2%
Partial response	15%	27%
Overall response	17%	29%
Failure-free survival	2.5 months	4.6 months
Median survival time	6.7 months	8.8 months
1-year survival	33%	37%

Of note, the confidence intervals overlapped in the 1-year survival data, but did not with failure-free survival or median survival time. While *P* values were not significant, Wilcoxson analysis favored survival outcome with combination chemotherapy.

Adverse effects were predictably more significant for the combination chemotherapy arm with combined grades 3 and 4 events of 90 vs 73 events in the single-agent arm. While grades 3 and 4 neutropenia were almost double the rate of that seen in the single-agent arm, there was no difference in the incidence of febrile neutropenic episodes. Subset analysis among elderly patients showed no statistically significant survival differences between treatment arms (Table 2).

Table 2. Elderly Subset Analysis in Single-Agent vs Combination Chemotherapy for NSCLC

Regimen	Paclitaxel	Paclitaxel + Carboplatin
Patient number	78	77
Overall response rate	21%	36%
Median survival time	5.8 months	8.0 months
1-year survival	31%	35%

Only lower performance score appeared to affect outcomes as indicated in Table 3.

Table 3. PS 2 Status and Treatment Outcome in NSCLC

Regimen	Paclitaxel	Paclitaxel + Carboplatin
Patient number	50	49
Overall response rate	10%	24%
Median survival time	2.4 months	4.7 months
1-year survival	10%	18%

In contrast, no significant difference in outcome was observed among patients with performance scores of 0 and 1, or in second-line treatment regimens whether patients received single or combination treatment. No quality-of-life differences were noted among 25 different assessment parameters, in spite of increased hematologic and nonhematologic adverse events, and no cost differences in emergency room, hospitalization, outpatient clinic, or prescription support were observed between single-agent and combination therapy. Dr. Lillenbaum concluded that combination therapy is probably superior to single-agent therapy in producing higher response rates and failure-free and median survival, but crossover is likely obscuring any differences in 1-year survival data, except for those patients with worse performance scores. Elderly patients with good performance status should be treated the same as their younger counterparts. Further study with more PS-2 patients needs to be conducted before definitive conclusions can be drawn.

Dr. Paul Bunn (incoming ASCO President) from the University of Colorado opened his commentary on Dr. Lillenbaum's presentation by reminding the audience of the national and international scope of lung cancer and lung cancer death, 90% of which is directly attributable to smoking. Old data have affirmed the value of platinum-based therapy in the treatment of NSCLC, while a relatively new drug like paclitaxel is certainly better than no drug at all. Recent studies have also demonstrated that 2 new drugs are superior to 1 old drug, albeit more costly. The current CALGB study confirms the findings of other recently published data that found combination gemcitabine/cisplatin superior to single-agent gemcitabine. Certainly no survival advantage has resulted from any modern cytotoxic 3-drug regimens, but adverse effects are significantly greater.

The addition of ZD1839 may change this thinking as reported during this meeting, but alternating doublets have failed to demonstrate any benefit. Previous studies, including a well-known Italian trial of vinorelbine vs best supportive care, support the current CALGB trial's conclusion that elderly patients with NSCLC should receive treatment. Moreover, previous studies have tended to exclude PS-2 patients, who clearly benefit as demonstrated by the CALGB data, in spite of increased but acceptable adverse event rates. The challenge will be to select 2 drug regimens that are safe in PS-2 patients, without sacrificing efficacy.

The value of second-line therapy has already been demonstrated in American and Canadian studies, and improvements in median survival time are associated with improved quality of life. Alternative biologic therapies or single agents may be more appropriate in this salvage setting. None of this will ever be sorted out unless clinicians "religiously" enroll their patients in clinical trials.

Reference

1. Lillenbaum R. Single agent versus combination chemotherapy in advanced NSCLC: a CALGB randomized trial of efficacy, quality of life and cost-effectiveness. Program and abstracts of the American Society of Clinical Oncology 38th Annual Meeting; May 18-21, 2002; Orlando, Florida. Abstract 2.

Source: Fred Hutchinson Cancer Research Center
Date: December 10, 1998

More on: Leukemia, Colon Cancer, Lung Cancer, Prostate Cancer, Lymphoma, Osteoporosis

Promising New Drug Uses Antibody Targeted Chemotherapy To Fight Leukemia

Science Daily — Scientists presented data here today at the 40th Annual Meeting of the American Society of Hematology (ASH), demonstrating how a breakthrough new experimental compound, known as CMA-676, uses an antibody connected to chemotherapy molecules to help patients fight a virulent and often fatal form of cancer - acute myelogenous leukemia (AML). The data appeared to confirm that this novel treatment method -- "antibody-targeted chemotherapy" -- shows promising efficacy and a more tolerable side effect profile than current chemotherapy treatments.

AML is a life-threatening disease in which certain white blood cells become cancerous and rapidly replace and destroy normal bone marrow and blood cells. AML is among the most serious forms of adult leukemia, with a relatively high fatality rate. Most patients require intensive chemotherapy to achieve complete remission, and some also must undergo bone marrow transplants. Up to half of patients with AML, even after such intensive treatment, have residual leukemic cells or experience a relapse.

Because current chemotherapy drugs to treat AML are non-specific - harming good as well as bad cells - patients who are receiving standard chemotherapy become very sick. Researchers at the Fred Hutchinson Cancer Research Center, in collaboration with scientists from thirteen leading leukemia centers including, University of Chicago Medical Center, MD Anderson Cancer Center and The University of Pennsylvania Cancer Center, are working with Wyoth-Ayerst Research and Celltech PLC to study CMA-676, an antibody-drug conjugate that delivers treatment directly to the leukemia cells.

The antibody is engineered to carry just a few molecules of a new and extremely potent chemotherapy agent - from the calicheamicin family – to selectively destroy leukemic blast cells. This approach may spare primary and vital bone marrow cells that are responsible for regenerating normal blood cells once the leukemia cells are destroyed.

A Phase I study of patients with advanced AML demonstrated early efficacy and defined the appropriate dosing regimen for Phase II studies. Promising data are now emerging from the current pivotal Phase II trial in the U.S. that involves patients following relapse after initial AML chemotherapy. A preliminary analysis of these data show that CMA-676 given alone produces a remission rate of approximately 40 percent - a rate comparable to that of standard combination chemotherapy regimens. These data also show that CMA-676 has other important advantages.

"The side effects are mild compared to standard chemotherapy," says Eric Sievers, M.D., of Fred Hutchinson Cancer Research Center. "Also, the treatment did not produce some of the more common chemotherapy-induced side effects."

Standard combination chemotherapy treatment produces significant major organ damage, and sores both in the mouth and in the intestinal tract (frequent sources for opportunistic infections). CMA-676 treatment does not produce these effects. As with all standard chemotherapy treatments, CMA-676 produces a temporary suppression of bone marrow and blood cell counts.

CMA-676 is administered as a single agent, in contrast with chemotherapy regimens that involve multiple drugs that increase the likelihood of adverse side effects and drug-drug interactions. It is administered in two IV infusions fourteen days apart, and many patients received it on an outpatient basis.

Similar studies of the new treatment are underway throughout Europe and Canada.

Note: This story has been adapted from a news release issued by Fred Hutchinson Cancer Research Center.

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